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Lung Cancer

Role of Targeted Therapy and Immune Checkpoint Blockers in Advanced Non-Small Cell Lung Cancer: A Review

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Non-small cell lung cancer • Molecular diagnostic testing • Personalized medicine

Abstract

Advanced non-small cell lung cancer (NSCLC) is a complex disease comprising molecularly distinct tumor types, each with a unique biology that is becoming increasingly better characterized. The aim of this review is to present an optimized treatment schema and the accompanying diagnostic testing approach for patients with advanced NSCLC. There are a number of therapies currently approved for patients with advanced NSCLC, including agents that target particular oncogenic drivers, as well as immune checkpoint blockers (ICBs) that elicit an antitumor response. Identification of genetic alterations (e.g., epidermal growth factor receptor, anaplastic lymphoma kinase, reactive oxygen species proto-oncogene 1, B-Raf proto-oncogene) or programmed cell death ligand-1 expression levels in NSCLC requires diligent molecular testing at initial diagnosis and, in some cases, at disease progression to ensure the most efficacious treatment is delivered. Accurate molecular diagnostic testing, along with the careful selection of currently approved targeted agents, ICBs, or systemic chemotherapy, provides therapy that is personalized according to patients' needs to achieve the best possible outcome. Enrollment in clinical trials that further the development of tailored therapies is highly recommended at all stages of treatment. ***The Oncologist*** 2019;24:1–15

Implications for Practice: Targeted therapies and immune checkpoint blockers provide effective and tailored options for patients with non-small cell lung cancer. Careful molecular analysis of tumor samples is necessary to identify the genetic alterations that are present, to ensure that each patient receives the most efficacious treatment for their specific tumor type. Personalized therapy provides each patient with the best probability for prolonged survival. Enrolling patients in clinical trials should be the first consideration before making each treatment decision.

Introduction

Non-small cell lung cancer (NSCLC) comprises 84% of all lung cancers [1]. Histologically, NSCLC is classified into two subtypes: nonsquamous cell carcinoma and squamous cell carcinoma (SCC). Within the nonsquamous category, adenocarcinoma is the predominant type, followed by large cell (undifferentiated) carcinoma and other rare cell types. Histologic classification of NSCLC is important for selection of therapy. In addition to histologic analysis, molecular characterization of tumors may identify genetic alterations for which targeted therapies or immune checkpoint blockers (ICBs) are available (Table 1). Identifying the genetic alterations that are present ensures that patients with NSCLC receive the most efficacious treatment for their specific tumor type.

The frequency of molecular alterations in NSCLC varies with tumor histology. In patients with lung adenocarcinoma, ∼60% of tumors contain a driver alteration [2]. Mutations in the epidermal growth factor receptor gene (*EGFR*) are found in ∼19% of patients with adenocarcinoma and in ∼3% of patients with squamous histology [3]. Rearrangements in the anaplastic lymphoma kinase gene (*ALK*) and the reactive oxygen species proto-oncogene 1 (*ROS1*) occur in ∼5% and 1% of NSCLC cases, respectively [4, 5]. Alterations in *EGFR*, *ALK*, *ROS1*, and the B-Raf proto-oncogene (*BRAF*) are not typically found in the same tumor, and each driver represents a distinct molecular subgroup of NSCLC with unique targeted therapy options. Targeted therapies for other rare genetic alterations are under investigation in the erb-b2 receptor tyrosine kinase 2 gene (*ERBB2*), the mesenchymal-epithelial transition gene (a prototypical receptor tyrosine kinase gene; *MET*), and the ret proto-oncogene (a receptor tyrosine kinase gene; *RET*), each of

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Table 1. Summary of data on efficacy and safety of targeted agents in metastatic NSCLC

Agent	Line	Approved for use	FDA-approved diagnostic test[a]	Pivotal trial	*n*	Median PFS (95% CI), mo [HR; *p*]	Median OS (95% CI), mo	AEs ≥20% (Grade 1–2)/ all AEs Grade ≥3[d]
					FDA-approved			
EGFR mutation								
Erlotinib	1	Patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations, as detected by an FDA-approved test [85]	cobas EGFR Mutation Test v2, Roche Molecular Systems, Inc. cobas EGFR Mutation Test, Roche Molecular Systems, Inc.	EURTAC [13]	86	9.7 (8.4–12.3)	19.3 (14.7–26.8)	Grade 1–2: rash (67%), diarrhea (52%), fatigue (51%), appetite loss (31%) Grade ≥3: rash (13%), diarrhea (5%), fatigue (6%)
Afatinib	1	Patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations, as detected by an FDA-approved test [86]	therascreen EGFR RGQ PCR Kit, Qiagen Manchester Ltd.	LUX-Lung 3 [14], LUX-Lung 6 [87]	LUX-Lung 3: 229 LUX-Lung 6: 242	LUX-Lung 3: 11.1 LUX-Lung 6: 11.0 (9.7–13.7)	LUX-Lung 3: NR LUX-Lung 6: 22.1 (20.0–NR)	LUX-Lung 3: Grade 1–2: rash/acne (73%), diarrhea (81%), dry skin (29%), stomatitis/mucositis (63%), paronychia (45%) Grade ≥3: rash/acne (16%), diarrhea (14%), stomatitis/mucositis (9%), paronychia (11%) LUX-Lung 6: Grade 1–2: rash/acne (66%), diarrhea (83%), stomatitis/mucositis (46%), paronychia (33%) Grade ≥3: rash/acne (15%), diarrhea (5%), stomatitis/ mucositis (5%)
Gefitinib	1	Patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations, as detected by an FDA-approved test [88]	cobas *EGFR* Mutation Test v2, Roche Molecular Systems, Inc. therascreen *EGFR* RGQ PCR Kit, Qiagen Manchester Ltd.	IPASS[b][12] IFUM [89]	IPASS: 609 IFUM: 106	IPASS: 5.7 IFUM: 9.7 (8.5–11.0)	IPASS: 18.6 IFUM: NR	IPASS: Grade 1–2: rash/acne (63%), diarrhea (43%), dry skin (24%), anorexia (20%) Grade ≥3: rash/acne (3.1%), diarrhea (4%) IFUM: Grade 1–2: rash (45%), diarrhea (27%) Grade ≥3: diarrhea (4%)
Osimertinib	1	Patients with metastatic *EGFR* T790M mutation-positive NSCLC, as detected by an FDA-approved test [51]	cobas *EGFR* Mutation Test v2, Roche Molecular Systems, Inc.[c]	FLAURA [15]	556	PFS: 18.9 (15.2–21.4) vs. erlotinib or gefitinib: 10.2 (9.6–11.1) [HR, 0.46; 95% CI, 0.37–0.57; $p < .0001$]	Interim analysis: NR vs. erlotinib or gefitinib: NR	Grade 1–2: rash/acne (57%), diarrhea (56%), dry skin (35%), paronychia (35%) Grade ≥3: rash/acne (1%), diarrhea (2%), dry skin (<1%), paronychia (<1%)
Osimertinib	2	Patients with metastatic *EGFR* T790M mutation-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR-TKI therapy [51]	cobas *EGFR* Mutation Test v2, Roche Molecular Systems, Inc.[c]	AURA2 [90] AURA Extension [91] AURA3 [52]	AURA2: 199 AURA Extension: 198 AURA3: 279	AURA2 PFS via BICR: 9.9 (8.5–12.3) AURA Extension: PFS: 12.3 (9.5–13.8) AURA3: 10.1 (8.3–12.3) vs. platinum-doublet chemotherapy: 4.4 (4.2–5.6) [HR, 0.30; 95% CI, 0.23–0.41; $p < .001$]	AURA2 DoR via BICR: 11.4 (9.0–NR) AURA Extension: NR AURA3: NR	AURA2: Grade 1–2: rash (40%), diarrhea (33%), paronychia (26%) Grade ≥3: rash (1%), diarrhea (<1%) AURA Extension: Grade 1–2: rash (39%), diarrhea (42%), paronychia (31%), dry skin (31%) Grade ≥3: rash (<1%), diarrhea (<1%) AURA3: Grade 1–2: rash (34%), diarrhea (41%), paronychia (22%), dry skin (23%) Grade ≥3: rash (1%), diarrhea (1%)
ALK rearrangement								
Crizotinib	1	Patients with metastatic NSCLC whose tumors are *ALK* positive, as detected by an FDA-approved test [92]	VENTANA ALK (D5F3) CDx Assay, Ventana Medical Systems, Inc. Vysis ALK Break Apart FISH Probe Kit, Abbott Molecular, Inc.	PROFILE 1014 [21]	172	10.9 (8.3–13.9) vs. chemotherapy 7.0 (6.8–8.2) [HR, 0.45; 95% CI, 0.35–0.60; $p < .001$]	NR	Grade 1–2: vision disorder (70%), diarrhea (59%), edema (48%), vomiting (44%), constipation (41%), upper respiratory infection (32%), abdominal pain (26%), dysgeusia (26%), increased transaminases (22%), headache (21%) Grade ≥3: vision disorder (1%), diarrhea (2%), edema (1%), vomiting (2%), constipation (2%), dysgeusia (26%), increased transaminases (14%), headache (1%)
Ceritinib	1	Patients with metastatic NSCLC whose tumors are *ALK* positive, as detected by an FDA-approved test [23]		ASCEND-4 [22]	376	16.6 (12.6–27.2) vs. chemotherapy 8.1 (5.8–11.1) [HR, 0.55; 95% CI, 0.42–0.73; $p < .00001$]	NR (29.3–NR) vs. chemotherapy 26.2 (22.8–NR)	Grade 1–2: diarrhea (80%), nausea (66%), vomiting (61%), increased ALT (29%), increased AST (36%), decreased appetite (33%), increased blood alkaline phosphatase (22%), fatigue (25%), abdominal pain (23%), cough (24%), decreased weight (20%), increased blood creatinine (20%) Grade ≥3: diarrhea (5%), nausea (3%), vomiting (5%), increased ALT (31%), increased AST (17%), increased gamma-glutamyltransferase (29%), decreased appetite (1%), increased blood alkaline phosphatase (7%), fatigue (4%), abdominal pain (2%), decreased weight (4%), increased blood creatinine (2%), upper abdominal pain (2%), noncardiac chest pain (1%), back pain (2%), asthenia (3%), dyspnea (2%), anemia (2%), neutropenia (1%)

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Table 1. (continued)

Agent	Line	Approved for use	FDA-approved diagnostic test[a]	Pivotal trial	*n*	Median PFS (95% CI), mo [HR; *p*]	Median OS (95% CI), mo	AEs ≥20% (Grade 1–2)/ all AEs Grade ≥3[d]
				FDA-approved				
Alectinib	1	Patients with metastatic NSCLC whose tumors are *ALK* positive [56]	VENTANA ALK (D5F3) CDx Assay	ALEX [24]	303	25.7 (19.9–NR) vs. crizotinib 10.4 (7.7–14.6) [HR, 0.47; 95% CI, 0.34–0.65; $p < .001$]		
Alectinib	2	Patients with metastatic NSCLC whose tumors are *ALK* positive and who have progressed on or are intolerant to crizotinib [56]	Not associated with an approved test, but tumors must have tested positive for *ALK* to have received first-line therapy	NP28761 [59] (North American) NP28673 (global)	NP28761: 69 NP28673: 138	ORR via IRC: NP28761, 48% (36–60) NP28673, 50% (41–59) PFS: NP28761, 8.1 (6.2–12.6) NP28673, 8.9 (5.6–11.3)	DoR via IRC: NP28761, 13.5 (6.7–NE) NP28673, 11.2 (9.6–NR)	NP28761: Grade 1–2: constipation (33%), fatigue (25%), peripheral edema (24%), myalgia (22%), nausea (22%), diarrhea (21%), headache (21%) Grade ≥3: dyspnea (3%), increased AST (2%), increased ALT (2%), fatigue (1%), peripheral edema (1%), myalgia (1%), asthenia (1%), headache (1%), vomiting (1%), diarrhea (1%) NP28673: Grade 1–2: fatigue (25%), constipation (33%), myalgia (22%), peripheral edema (24%) Grade ≥3: fatigue (1%), myalgia (1%), peripheral edema (1%)
Ceritinib	2	Patients with *ALK*-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib [23]	Not associated with an approved test, but tumors must have tested positive for *ALK* to have received first-line therapy	ASCEND-1 [58]	163	PFS: 6.9 (5.6–8.7); ORR via IA: 56% (49–64%)	DoR 8.3 (6.8–8.7)	Grade 1–2: diarrhea (80%), nausea (77%), vomiting (57%), abdominal pain (37%), fatigue (38%), decreased appetite (36%), constipation (30%), cough (29%), abdominal pain upper (23%), dyspnea (21%), back pain (20%), increased aspartate aminotransferase (23%) Grade ≥3: diarrhea (6%), nausea (6%), vomiting (4%), abdominal pain (1%), fatigue (5%), decreased appetite (2%), dyspnea (4%), back pain (<1%), increased aspartate aminotransferase (10%)
Brigatinib	2	Patients with *ALK*-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib [93]	Not associated with an approved test, but tumors must have tested positive for *ALK* to have received first-line therapy	ALTA [61]	90 mg qd: 109 90 mg then 180 mg qd: 110	90 mg qd: 9.2 (7.4–15.6) 90 mg–>180 mg qd: 12.9 (11.1–NR)	Probability of OS at 1 year: 90 mg qd: 71% 90 mg–>180 mg qd: 80%	90 mg qd: Grade 1–2: nausea (32%), diarrhea (19%), vomiting (22%), fatigue (27%), dyspnea (24%), headache (28%), decreased appetite (21%) Grade ≥3: nausea (<1%), vomiting (2%), constipation (<1%), fatigue (2%), dyspnea (3%), ILD/pneumonitis (2%), peripheral neuropathy (<1%), rash (2%), hypertension (6%), back pain (2%), arthralgia (<1%), decreased appetite (<1%), pneumonia (3%) 90 mg–>180 mg qd: Grade 1–2: nausea (39%), diarrhea (38%), vomiting (23%), fatigue (36%), cough (34%), headache (26%), rash (24%) Grade ≥3: nausea (<1%), pyrexia (<1%), dyspnea (2%), ILD/pneumonitis (3%), hypoxia (3%), headache (<1%), peripheral neuropathy (2%), rash (4%), hypertension (6.4%), back pain (2%), myalgia (<1%), pain in extremity (<1%), decreased appetite (<1%), pneumonia (6%)
Lorlatinib	2	Patients ALK-positive metastatic NSCLC who have progressed on crizotinib and ≥1 other ALK inhibitor, or alectinib or ceritinib as the first ALK inhibitor therapy [63]	Not associated with an approved test, but tumors must have tested positive for *ALK* to have received first-line therapy	Study B7461001	215 ALK+	ORR, overall: 48% (95% CI, 42–55); previous crizotinib and ≥1 ALK inhibitor: 39% (95% CI, 30–48); previous alectinib only: 31% (95% CI, 9–61); previous ceritinib only: 46% (95% CI, 19–75)	mDOR, overall: 12.5 months (95% CI, 8.4–23.7)	Grade 1–2: mood effects (21%), peripheral neuropathy (44%), cognitive effects (25%), dyspnea (22%), diarrhea (21%), arthralgia (22%), edema (54%), fatigue (26%), weight gain (20%) Grade 3: mood effects (2%), peripheral neuropathy (3%), cognitive effects (2%), dyspnea (5%), diarrhea (1%), arthralgia (1%), edema (3%), fatigue (<1%), weight gain (4%)
ROS1 rearrangement								
Crizotinib	1	Patients with metastatic NSCLC whose tumors are *ROS1*-positive [92]	Not associated with an approved test	PROFILE 1001	50	19.3 (95% CI, 14.8–NR)	Probability of survival at 12 months: 79% (95% CI, 65–88)	Grade 1–2: vision disorders (85%), nausea (49%), edema (45%), diarrhea (42%), vomiting (38%) Grade 3: hypophosphatemia (13%), neutropenia (9%), increased transaminases (4%) [no grade 4 TRAE]
BRAF V600E4								
Dabrafenib + trametinib	1	Patients with metastatic NSCLC whose tumors are *BRAF* V600E4-positive [31]	Oncomine Dx Target Test, Thermo Fisher Scientific	Study BRF113928 (NCT01336634)	93	ORR via IRC: *n* = 36; 61% (95% CI, 44–77)	Responders with DoR ≥6 months: *n* = 22, 59%	Grade 1–2: increased blood alkaline phosphatase (64%), hyperglycemia (62%), increased AST (57%), pyrexia (50%), fatigue (46%), nausea (45%), leukopenia (40%), hyponatremia (40%), anemia (36%), neutropenia (36%), vomiting (30%), diarrhea (30%), dry skin (30%), decreased appetite (29%), hypophosphatemia (29%), edema (28%), lymphopenia (28%), increased ALT (26%), rash (25%), chills (22%), cough (22%),

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Table 1. (continued)

Agent	Line	Approved for use	FDA-approved diagnostic test[a]	Pivotal trial	*n*	Median PFS (95% CI), mo [HR; *p*]	Median OS (95% CI), mo	AEs ≥20% (Grade 1–2)/ all AEs Grade ≥3[d]
FDA-approved								
								increased creatinine (20%), hemorrhage (20%) Grade ≥3: hyponatremia (17%), lymphopenia (14%), anemia (10%), hyperglycemia (9%), leukopenia (8%), neutropenia (8%), hypophosphatemia (7%), increased AST (4%), increased ALT (6%), dyspnea (5%), pyrexia (5%), fatigue (5%), vomiting (3%), rash (3%), hemorrhage (3%), diarrhea (2%), creatinine increased (1%), chills (1%), dry skin (1%)
Preliminary data for targeted agents in development								
MET amplification or *MET* exon 14 skipping								
Crizotinib		Investigational phase I [94]	—[e]	NCT00585195	12		mDoR: 35 (16–112)	Most common all grade: diarrhea (50%), nausea (31%), vomiting (31%), peripheral edema (25%), visual impairment (25%)
RET rearrangements								
Cabozantinib		Investigational phase II [95]	—[e]	NCT01639508	25	28% (12–49)		Grade ≥3: lipase elevation (15%), increased alanine aminotransferase (8%), increased aspartate aminotransferase (8%), decreased platelet count (8%), hypophosphatemia (8%)
Vandetanib		Investigational phase II [96]	—[e]	LURET trial (UMIN000010095)	17	ORR: 53% (28–77); PFS: 4.7 (2.8–8.5)		Grade ≥3: hypertension (58%), diarrhea (11%), rash (16%), dry skin (5%), QT prolongation (11%)
Lenvatinib		Investigational phase II [97]	—[e]	NCT01877083	25	ORR: 16%; PFS: 7.3 (3.6–10.2)		Grade ≥3: hypertension (68%), nausea (60%), decreased appetite (52%), diarrhea (52%), proteinuria (48%), vomiting (44%)
HER2								
Ado-trastuzumab emtansine		Investigational phase II basket [98]	—[e]	NCT02675829	18	ORR: 44% (22–69); PFS: 4 (3.0–NR)	mDoR: 5 (3.0–NR)	TRAE: Grade 1–2: infusion reaction (28%), fatigue (33%), thrombocytopenia (33%), increased AST or ALT (39%) Grade 3: anemia (6%)
Ado-trastuzumab emtansine	2	Investigational phase II [99]	—[e]	NCT02289833	49	ORR: 20% (5.7–43.7); PFS: 2.6 (1.4–2.8)	mDoR: 7.3 (2.9–8.3); OS: 12.2 (5.2–NR)	Grade ≥3: fatigue (4%), dyspnea (4%), seizure (2%), infusion-related reaction (2%), thrombocytopenia (1%)
Afatinib	2	Investigational phase II [100]	—[e]	NICHE, NCT02369484	13	PFS: 15.9 (12.0–48.0)	Study closed early	Grade 1–2: diarrhea (92%), oral mucositis (23%), abdominal pain (23%), vomiting (23%), erythema multiforme (31%), acneiform rash (31%), dry skin (23%), paronychia (38%), fatigue (31%) Grade ≥3: oral mucositis (8%), dyspnea (16%), epistaxis (8%), pleural effusion (8%), increased gamma-glutamyltransferase (8%), dehydration (8%), hyperkalemia (8%), hyponatremia (8%), urinary tract obstruction (8%), anemia (8%), febrile neutropenia (8%)
Trastuzumab + paclitaxel	2	Investigational phase II [101]	—[e]	NCT02226757	24	ORR: 46%	mDoR: 8.4 (3.6–13.3); OS: 36 (32.4–39.6)	Grade 1–2: fatigue (38%), myalgia (42%), dyspnea (29%), neuropathy (21%), headache (25%), constipation (21%), nausea (21%) Grade ≥3: fatigue (4%), neuropathy (4%), decreased neutrophil count (4%), pneumonitis (4%), urinary tract infection (4%)

[a]http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm.
[b]Patient population was not selected for *EGFR*-sensitizing mutations.
[c]Samples can be formalin-fixed, paraffin-embedded tissue, or plasma ctDNA.
[d]Grade 1/2 events are listed if they occurred in ≥20%; all grade ≥3 are listed.
[e]Not associated with an approved test.
Abbreviations: AE, adverse event; *ALK*, anaplastic lymphoma kinase gene; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BICR, blinded independent review committee; *BRAF*, B-Raf proto-oncogene; CI, confidence interval; ctDNA, circulating tumor; DoR, duration of response; *EGFR*, epidermal growth factor receptor; FDA, U.S. Food and Drug Administration; *HER2*, human epidermal growth factor receptor 2 gene; HR, hazard ratio; IA, investigator assessment; ILD, interstitial lung disease; IRC, independent review committee; IRR, independent radiology review; *MET*, mesenchymal-epithelial transition gene; mDoR, median duration of response; NE, not estimable; NR, not reached; NSCLC, non-small cell lung cancer; ORR: objective response rate; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival; qd, once a day; *RET*, ret proto-oncogene; *ROS1*, reactive oxygen species proto-oncogene 1; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse event.

which is found in ≤3% of patients with lung adenocarcinoma (Table 1) [6]. The most common mutation for which no targeted therapy is available is a Kirsten ras oncogene homolog gene (*KRAS*) mutation, which occurs in ∼25% of adenocarcinoma [2, 7]. Although targeted agents are available for many patients with adenocarcinoma, targeted therapies are very rarely suitable for patients with SCC [7].

In addition to oncogenic driver mutations, tumor cell evasion of the immune system can also lead to carcinogenesis. Some tumor cells can exploit inhibitory immune checkpoints regulated by programmed cell death-1 receptor (PD-1) and programmed cell death ligand-1 (PD-L1) through expression of PD-L1 on the tumor cell to prevent T cell activation. An analysis of three global clinical trials involving 4,784 patients with NSCLC found that 66% of all tumors had measurable PD-L1 expression [8]. When separated by histology, 74% of patients with non-squamous histology and 81% of patients with squamous histology had measurable PD-L1 expression [8]. The monoclonal

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antibodies anti-PD-1, anti-PD-L1, and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are ICBs that act to resensitize suppressed immune cells and have been a focus of drug development. Recently, anti-PD-1 and anti-PD-L1 agents were approved for patients with advanced NSCLC (Table 2) [9–11].

NSCLC Treatment Paradigm

Targeted therapies and ICBs provide effective and tailored options for patients with NSCLC. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer V.1.2019 recommend that all patients with metastatic adenocarcinoma should have their tumor tissue tested for actionable driver mutations [7]. Patients with squamous histology should be tested if the patient has never been a smoker or has mixed histologies or at the discretion of the treating physician. The order of molecular testing and corresponding use of these agents are very important in the treatment of NSCLC. For example, testing for actionable targets (i.e., *EGFR*, *ALK, ROS1*, and *BRAF* V600E) should be conducted first, before PD-L1 expression, because patients with positive tests for *EGFR* mutations and *ALK* rearrangements have high response rates to tyrosine kinase inhibitors (TKIs) but low response rates to PD-L1 antibodies.

Here, we provide testing and treatment schemata (Figs. 1–3), inclusive of recent U.S. Food and Drug Administration (FDA) approvals, that summarize how to identify and treat different populations of patients with NSCLC (Fig. 1, targeted therapies; Fig. 2, immunotherapeutic agents; Fig. 3, therapies for patients ineligible for targeted therapy or immunotherapy). Note that some of these agents are not recommended by NCCN for various reasons, including if the drugs have not yet been FDA approved for NSCLC.

Nonsquamous Histology: First-line Targeted Therapies

First-line, FDA-approved agents for patients with advanced or metastatic NSCLC with mutations in *EGFR* (exon 19 deletions, exon 21 L858R substitution, as detected by an FDA-approved test) include the EGFR-TKIs gefitinib, erlotinib, afatinib, and osimertinib (Table 1). Gefitinib, erlotinib, and afatinib are selective for *EGFR*-sensitizing mutations; osimertinib is selective for both *EGFR*-sensitizing and *EGFR* T790M resistance mutations. In the patient population that is *EGFR* mutation-positive, these agents have a response rate of approximately 70%, have successfully extended the median progression-free survival (PFS) by about 1 year, and have a median overall survival (OS) of approximately 19 months [12–15]. Osimertinib significantly improved PFS compared with gefitinib or erlotinib in FLAURA [15]. Osimertinib is the agent of choice not only because of its superior efficacy but also because of its mild toxicity profile and ability to treat and delay brain metastases. Based on results from the FLAURA trial, osimertinib is recommended by NCCN as the preferred first-line option in patients with locally advanced or metastatic NSCLC who have sensitizing *EGFR* mutation [7]. The EGFR-TKI dacomitinib significantly improved PFS [16] and OS [17] compared with gefitinib in ARCHER 1050. Dacomitinib recently received FDA approval, but this is unlikely to change current practice.

Combination therapies are being assessed. Gefitinib in combination with carboplatin plus pemetrexed increased median OS (52.2 vs. 38.8 months; $p = .013$) and PFS (20.9 vs. 11.2 months; $p < .001$), but not PFS2 (20.9 vs. 21.1 months; $p = .806$), compared with gefitinib alone, in NEJ009 [18]. Addition of bevacizumab to erlotinib therapy increased median PFS (16.0 vs. 9.7 months; $p = .0015$) [19], but not OS [20], in JO25567. However, with osimertinib being the agent of choice, studies must be conducted with osimertinib combinations versus single-agent osimertinib.

Patients with *ALK* rearrangement-positive NSCLC benefit from ALK TKIs (crizotinib, ceritinib, alectinib; Table 1) [21, 22]. Crizotinib is an ALK, ROS1, and MET inhibitor; ceritinib inhibits ALK and IGF-R1; and alectinib inhibits ALK and RET. Crizotinib is FDA approved for first-line use in patients with *ALK*-rearranged, locally advanced, or metastatic NSCLC based on the PROFILE 1014 trial that demonstrated significantly longer median PFS with crizotinib compared with chemotherapy (10.9 vs. 7.0 months; $p < .001$) [21]. Ceritinib was recently approved in the first line in *ALK*-rearranged NSCLC based on the phase III ASCEND-4 trial [23]. Ceritinib-treated patients had significantly longer median PFS compared with the chemotherapy group (16.6 vs. 8.1 months; $p < .00001$) [22]. Furthermore, alectinib has recently been FDA approved and is recommended by NCCN as the preferred first-line option (category 1) in patients with metastatic, *ALK*-rearranged NSCLC based on the phase III ALEX study that found a significantly longer median PFS with alectinib compared with patients receiving crizotinib (25.7 vs. 10.4 months; $p < .001$) and on its ability to treat and delay brain metastases [24]. In a recent first interim analysis from ALTA-1L, brigatinib increased estimated 12-month PFS compared with crizotinib (67% vs. 43%; $p < .001$) in patients with *ALK*-rearranged NSCLC who had not previously received ALK inhibitors [25, 26]. Frontline phase III trials of lorlatinib or ensartinib versus crizotinib are ongoing.

For patients with *ROS1*-rearranged NSCLC, crizotinib is FDA approved for first-line use based on the PROFILE 1001 phase I study (Table 1) [27, 28]. Of the 53 patients with *ROS1* rearrangements who were treated with crizotinib, the median PFS was 19.3 months, and the probability of survival at 6 and 12 months was 91% and 79%, respectively [27]. In a recent phase II study in 28 patients with NSCLC and *ROS1* rearrangements who were treated with ceritinib, the median PFS with ceritinib was 9.3 months [29]. Crizotinib is recommended by NCCN as the preferred first-line option over ceritinib for patients with *ROS1*-rearranged NSCLC, based on the trial data and the FDA approval [7]. Therapy with entrectinib in *ROS1*-rearranged NSCLC is being assessed [30].

The BRAF inhibitor dabrafenib in combination with trametinib is FDA approved for first-line use in patients with advanced or metastatic NSCLC who are *BRAF* V600E-mutation positive [31]. In the phase II BRF113928 study, the overall response rate (ORR) was 61% in the first-line cohort ($n = 36$) and 63% in patients who had received at least one previous platinum regimen ($n = 57$) [31].

For driver mutations without corresponding approved targeted therapies for metastatic NSCLC (e.g., *MET*, *RET,* and human epidermal growth factor receptor 2 [*HER2*]), NCCN recommends (category 2A) using targeted agents approved in other indications or a clinical trial for the corresponding agent,

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Table 2. Summary of data on efficacy and safety of ICBs approved for use in metastatic NSCLC

Agent	Line	Approved for use	Diagnostic test	Pivotal trial	*n*	Median PFS (95% CI), mo	Median OS (95% CI), mo	AEs ≥10% (Grade 1–2)/ Grade ≥3
PD-1								
Pembrolizumab + pemetrexed + carboplatin	1	Patients with metastatic nonsquamous NSCLC [9]	NA	KEYNOTE-021 Cohort G1 [40]	123	13.0 (8.3–NR) vs. carboplatin/pemetrexed 8.9 (4.4–10.3). [HR, 0.53; 95% CI, 0.31–0.91; $p = .010$]	NR (NR–NR)	Grade 1–2: fatigue (68%), peripheral edema (22%), nausea (66%), constipation (51%), vomiting (37%), diarrhea (35%), rash (40%), pruritus (24%), alopecia (20%), dyspnea (36%), cough (24%), decreased appetite (31%), headache (31%), dizziness (24%), dysgeusia (20%), insomnia (24%), upper respiratory tract infection (20%), arthralgia (15%) Grade ≥3: fatigue (3%), nausea (2%), vomiting (2%), diarrhea (2%), rash (2%), dyspnea (3%)
Pembrolizumab + carboplatin + nab-paclitaxel or paclitaxel	1	Patients with metastatic squamous NSCLC [9]	NA	KEYNOTE-407 [72]	559	6.4 (6.2–8.3) vs. carboplatin/(nab) paclitaxel 4.8 (4.3–5.7). [HR, 0.56; 95% CI, 0.45–0.70; $p < .001$]	15.9 (13.2–NR) vs. carboplatin/(nab) paclitaxel 11.3 (9.5–14.8). [HR, 0.64; 95% CI, 0.49–0.85; $p < .001$]	Grade 1–2: anemia (38%), alopecia (46%), neutropenia (15%), nausea (35%), thrombocytopenia (23.8%), diarrhea (30%), decreased appetite (22%), constipation (22%), fatigue (20%), asthenia (19%), arthralgia (19%), peripheral neuropathy (19%), vomiting (16%), cough (13%), dyspnea (12%) Grade ≥3: anemia (16%), alopecia (0.4%), neutropenia (23%), nausea (1%), thrombocytopenia (7%), diarrhea (4%), decreased appetite (2%), constipation (<1%), fatigue (3%), asthenia (2%), arthralgia (1%), peripheral neuropathy (1%), vomiting (0.4%), cough (<1%), dyspnea (1%)
Pembrolizumab	1	Patients with metastatic NSCLC whose tumors have high PD-L1 expression (TPS ≥50%) as determined by an FDA-approved test, with no *EGFR* or *ALK* genomic tumor aberrations, and no previous systemic chemotherapy treatment for metastatic NSCLC [9]	PD-L1 IHC 22C3 pharmDx test	KEYNOTE-024 [34]	305	10.3 (6.7–NR) vs. platinum combination 6.0 (4.2–6.2) $p < .001$	NR (NR–NR)	Grade 1–2: diarrhea (10%), pyrexia (10%), fatigue (11%), nausea (10%) Grade ≥3: diarrhea (4%), anemia, fatigue (1%), vomiting, pneumonitis, severe skin reaction (4%), colitis (1%), hypophysitis (<1%), nephritis (<1%), pancreatitis (<1%), type 1 diabetes mellitus (<1%)
Pembrolizumab	2	Patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations before receiving pembrolizumab [9]	PD-L1 IHC 22C3 pharmDx test	KEYNOTE-010 [67]	2 mg/kg: 139. 10 mg/kg: 151	2 mg/kg: 3.9 (3.1–4.1) 10 mg/kg: 4.0 (2.7–4.3) vs. docetaxel 4.0 (3.1–4.2)	2 mg/kg: 10.4 (9.4–11.9) [0.71 (95% CI, 0.58–0.88; $p = .0008$)] 10 mg/kg: 12.7 (10.0–17.3) [0.61 (0.49–0.75; $p < .0001$)] vs. docetaxel 8.5 (7.5–9.8)	(2 mg/kg): Grade 1–2: fatigue (13%), decreased appetite (13%), nausea (11%); Grade ≥3: fatigue (1%), decreased appetite (1%), nausea (<1%) (10 mg/kg):Grade 1–2: fatigue (14%), rash (13%) decreased appetite (10%); Grade ≥3: fatigue (2%), rash (<1%), decreased appetite (<1%)
Nivolumab	2	Patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations before receiving nivolumab [10]	PD-L1 IHC 28-8 pharmDx	SQ: CheckMate-017 [76] NSQ: CheckMate-057 [65]	CheckMate-017: 135 CheckMate-057: 292	CheckMate-017: 3.5 (2.1–4.9) CheckMate-057:2.3 (2.2–3.3)	CheckMate-017: 9.2 (7.3–13.3) vs. docetaxel 6.0 (8.1–10.7) [HR, 0.59; 95% CI, 0.44–0.79; $p < .001$] CheckMate-057: 12.2 (9.7–15.0)	CheckMate-017: grade 1–2: fatigue (15%), asthenia (10%), decreased appetite (10%); Grade ≥3: fatigue (1%), decreased appetite (1%) CheckMate-057: Grade 1–2: fatigue (15%), nausea (11%), asthenia (10%), decreased appetite (10%); Grade ≥3: fatigue (1%), nausea (1%), asthenia (<1%)
PD-L1								
Atezolizumab	2	Patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations before receiving atezolizumab [11]	VENTANA PD-L1 (SP142) Assay	OAK [69]	425	2.8 (2.6–3.0)	13.8 (11.8–15.7)	Grade 1–2: fatigue (24%), decreased appetite (23%), cough (23%) Grade ≥3: fatigue (3%)

Abbreviations: AE, adverse event; *ALK*, anaplastic lymphoma kinase gene; CI, confidence interval; *EGFR*, epidermal growth factor receptor; FDA, U.S. Food and Drug Administration; HR, hazard ratio; ICB, immune checkpoint blocker; IHC, immunohistochemistry; NA, not applicable; NR, not reached; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; OS, overall survival; PD-1, programmed cell death-1 receptor; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; SQ, squamous; TPS, tumor proportion score.

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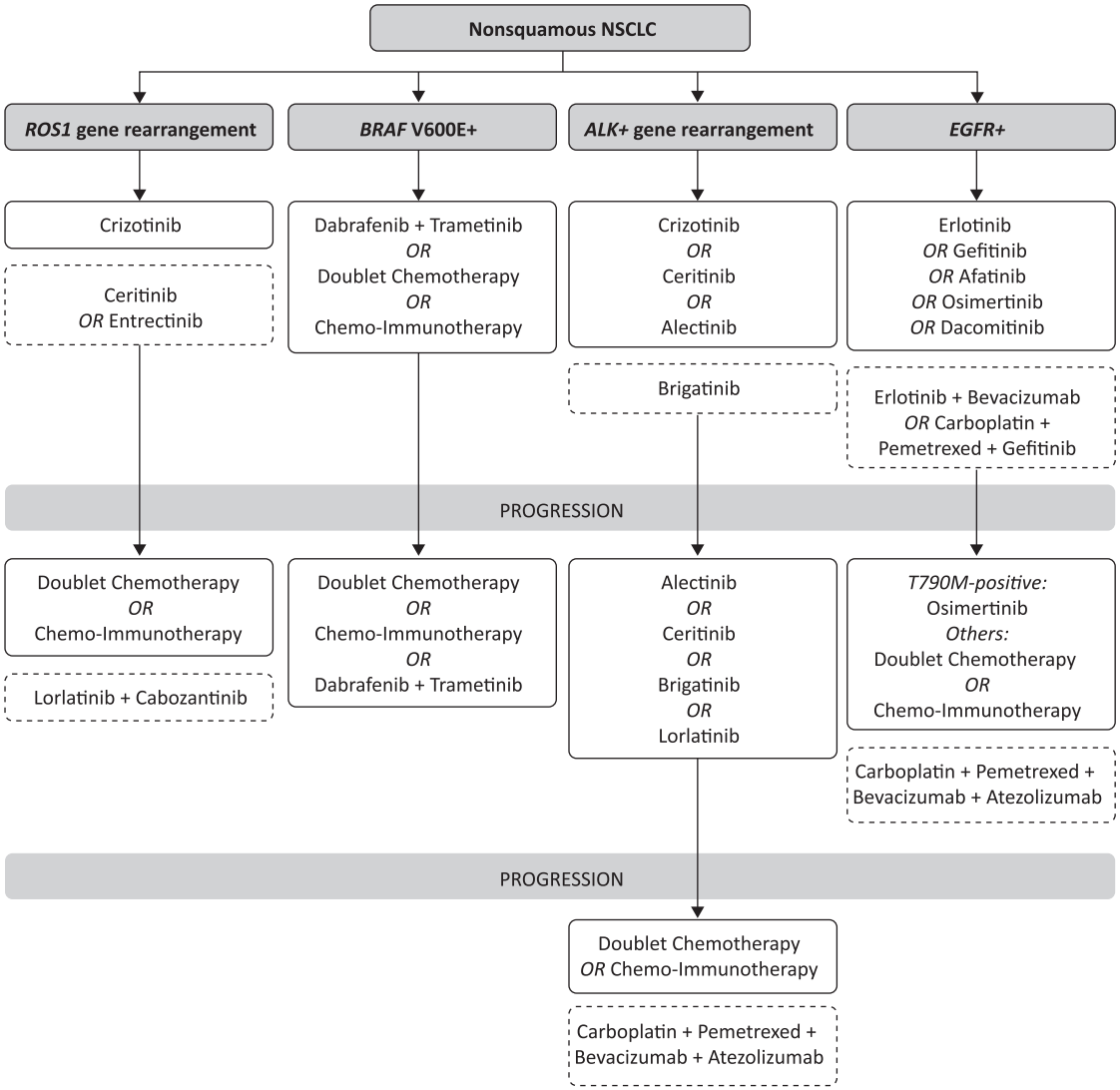

Figure 1. Therapies for patients with NSCLC eligible for targeted therapies. Boxes with the dashed lines contain those drugs which are not yet U.S. Food and Drug Administration (FDA) approved. Please see the text for treatment options for other actionable mutations. Note that some of these agents are not recommended by NCCN for various reasons, including if the drugs have not yet been FDA approved for NSCLC.
Abbreviations: *ALK*, anaplastic lymphoma kinase; *BRAF*, B-Raf proto-oncogene; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; *ROS1*, reactive oxygen species proto-oncogene 1.

if available [7]. Early-phase clinical trials have shown promising results with the RET inhibitors LOXO-292 and BLU-667 [32, 33]. Among 30 patients with RET-positive NSCLC treated with LOXO-292 in a phase I/II study, the ORR was 77% [32]. BLU-667 demonstrated antitumor activity in a phase I study in patients with RET-altered solid tumors, including NSCLC [33]. The question remains: what is the optimal time to administer targeted therapies that have not yet been approved for use in NSCLC? Most of the data support their use in the second line or beyond.

Nonsquamous Histology: First-Line ICBs

When no actionable alterations are detected, ICBs have a role in the treatment of metastatic NSCLC (Table 2). Monotherapy with the PD-1 receptor inhibitor pembrolizumab gained first-line approval based on the phase III KEYNOTE-024 study of patients with metastatic NSCLC and high PD-L1 expression (≥50% tumor proportion score [TPS]), with no *EGFR* or *ALK* alterations (n = 305; Table 2) [9, 34]. First-line pembrolizumab significantly extended median PFS (10.3 vs. 6.0 months; $p < .001$) and OS (estimated 6-month OS rate of 80.2% vs. 72.4%; $p = .005$) compared with platinum-based chemotherapy [34]. Significance was maintained within the nonsquamous subset (n = 249) [34]. Pembrolizumab lacks efficacy in TKI-naive patients with *EGFR* mutations [35]. Recent results from the KEYNOTE-042 trial confirm OS benefits with pembrolizumab in patients with PD-L1 expression levels ≥1% (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.71–0.93; $p = .0018$) [36]. This is of particular interest in light of the CheckMate-026 results that showed that patients with NSCLC and PD-L1 expression levels ≥5% who were treated with nivolumab monotherapy did not improve their PFS compared with those treated with chemotherapy (4.2 vs. 5.9 months) [37]. However, the benefit in KEYNOTE-042 was driven by the ≥50%

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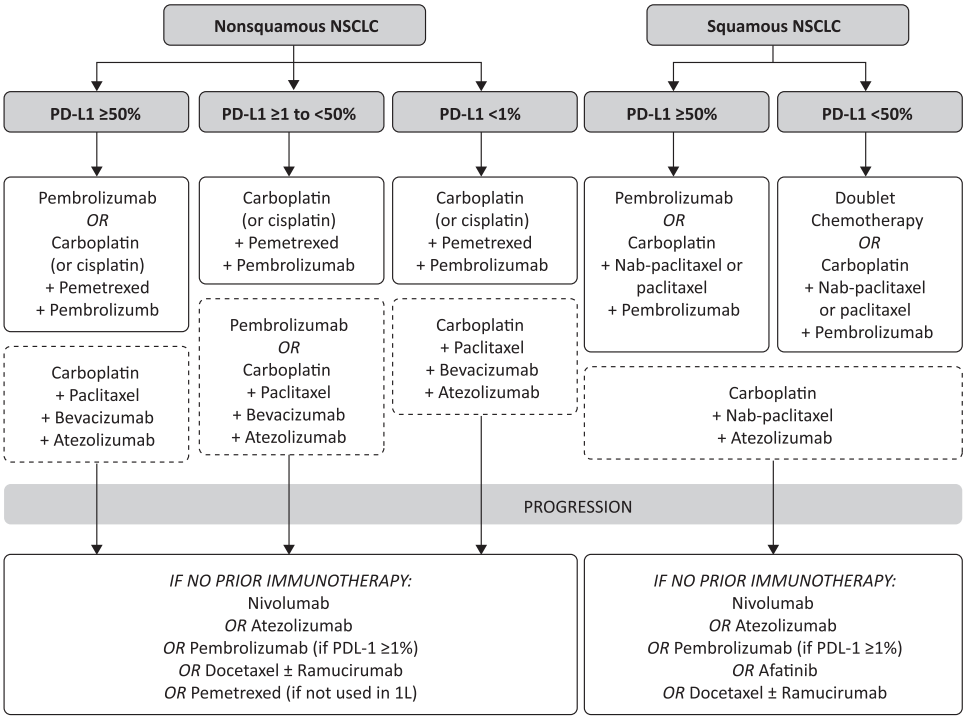

Figure 2. Immunotherapeutic agents for patients with NSCLC ineligible for targeted therapy. Boxes with the dashed lines contain those drugs which are not yet U.S. Food and Drug Administration (FDA) approved. Note that some of these agents are not recommended by NCCN for various reasons, including if the drugs have not yet been FDA approved for NSCLC.
Abbreviations: NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1.

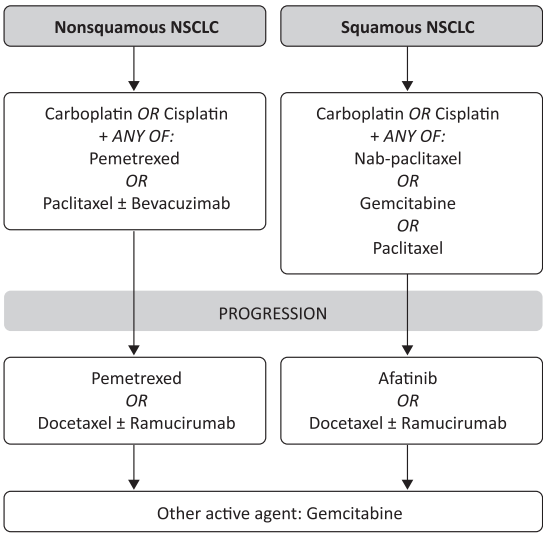

Figure 3. Therapies for patients with NSCLC ineligible for targeted therapy or immunotherapy. Note that NCCN recommends many regimens for metastatic nonsquamous or squamous NSCLC; this is an incomplete list. Some of these agents are not recommended by NCCN.
Abbreviation: NSCLC, non-small cell lung cancer.

PD-L1 expression group. The role of tumor mutation burden (TMB) as a predictive biomarker is being assessed as part of the CheckMate 227 trial, with initial results showing increased PFS with nivolumab plus ipilimumab versus platinum-doublet chemotherapy in patients with 10 or more mutations per megabase (mut/Mb) compared with those with fewer than 10 mut/Mb [38]. More data are needed to assess whether TMB is a viable biomarker for predicting beneficiaries of therapy; currently, it is neither FDA approved nor ready for clinical use.

Pembrolizumab was granted accelerated approval for use in metastatic nonsquamous NSCLC in combination with pemetrexed and carboplatin, independent of PD-L1 expression [39]. The approval is based on results from KEYNOTE-021 in which 123 patients received either carboplatin plus pemetrexed plus pembrolizumab or carboplatin plus pemetrexed alone as a first-line regimen and showed that the addition of pembrolizumab significantly extended PFS (13.0 vs. 8.9 months; $p = .010$) [40]. However, OS data are pending, and it remains unclear if giving an ICB concurrently is superior to using a sequential approach. Pembrolizumab in combination with pemetrexed and platinum was recently granted FDA approval as first-line therapy, based on KEYNOTE-189 trial data, which showed PFS and OS benefits with pembrolizumab plus pemetrexed plus carboplatin (or cisplatin) compared with pemetrexed plus carboplatin (or cisplatin) alone [41]. Many other ICBs are being evaluated in phase III clinical trials in the first-line setting as monotherapy or dual therapy, or in combination with chemotherapy (Table 3). Atezolizumab in combination with carboplatin plus paclitaxel plus bevacizumab significantly increased PFS compared with carboplatin plus paclitaxel plus bevacizumab alone in IMpower150 (19.2 vs. 14.7 months; HR, 0.78; 95% CI, 0.64–0.96; $p = .016$) [42], and the combination was recently granted priority FDA review.

Nonsquamous Histology: First-Line Chemotherapy

Chemotherapy is a first-line intervention when no actionable biomarkers are detected and when pembrolizumab is not

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suitable for the patient [7]. Pemetrexed plus a platinum-based chemotherapy is the most common regimen, but other platinum doublets are available. This combination is recommended based on a phase III study of patients with advanced NSCLC, in which the subanalysis of 1,000 patients with nonsquamous histology found a statistically significant improvement in OS in patients who received the cisplatin plus pemetrexed combination versus cisplatin plus gemcitabine (11.8 vs. 10.4 months; HR, 0.81; $p = .005$) [43]. Pemetrexed maintenance therapy is also used in this population based on the PARAMOUNT study, which found a significant reduction in the risk of disease progression (HR, 0.62; $p < .0001$), improved OS (HR, 0.78; $p = .0195$), and increased PFS, 4.1 months (95% CI, 3.2–4.6) versus 2.8 months (95% CI, 2.6–3.1), compared with placebo [44, 45]. A combination of carboplatin, paclitaxel, and bevacizumab can be used in selected patients with nonsquamous NSCLC based on significant improvements in the median OS (12.3 vs. 10.3 months; HR, 0.79; $p = .003$) and PFS (6.2 vs. 4.5 months; HR, 0.66; $p < .001$) compared with chemotherapy alone [46]. Bevacizumab should be considered for patients without hemoptysis, cavitary, or central tumors; however, patients with treated brain metastases can be included for treatment with bevacizumab.

Nonsquamous Histology: Second-Line Targeted Therapies

Rebiopsy is recommended for patients who progress on a first-line targeted therapy, as it may indicate the mechanism of drug resistance. The most commonly acquired resistance mechanism to first- and second-line EGFR-TKIs is the *EGFR* T790M mutation, which occurs in ∼60% of cases [47–50]. Only osimertinib is approved for use in patients with metastatic *EGFR* T790M mutation-positive NSCLC, as detected by an FDA-approved liquid biopsy or tumor test, who have progressed on or after EGFR-TKI therapy with erlotinib, afatinib, or gefinitib [51]. The AURA3 phase III trial found osimertinib to improve PFS significantly (10.1 vs. 4.4 months; $p < .001$) versus a platinum-based doublet chemotherapy [51, 52]. Osimertinib is also a category 1 recommendation for patients with metastatic NSCLC who have *EGFR* T790M mutation and symptomatic brain metastases [7]. As third-line treatment in *EGFR* T790M mutated NSCLC, PFS with osimertinib was 10.20 months compared with 2.95 months with docetaxel-bevacizumab in a recently completed phase III trial [53].

With osimertinib moving to the first-line setting, many mechanisms of resistance are emerging. If an actionable mutation is found, the appropriate inhibitor may be tried, or, in the case of transformation to small cell lung cancer, the patient should be treated with etoposide plus platinum. Otherwise, combination chemotherapy is the treatment of choice.

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combination chemotherapy is the treatment of choice. In an *EGFR*/*ALK* mutation subgroup analysis of IMPower150, OS was not reached in patients treated with atezolizumab plus bevacizumab plus chemotherapy, compared with an OS of 17.5 months for those treated with bevacizumab plus chemotherapy [42]. Upon progression, disease flare occurs in 9%–23% of patients when the EGFR-TKI therapy is discontinued [54, 55]. Therefore, continuation of EGFR-TKI therapy until immediately before starting an appropriate second-line regimen is recommended.

The ALK inhibitors ceritinib, alectinib, and brigatinib are three FDA-approved, second-line options for patients with *ALK* rearrangements who have progressed and are crizotinib-resistant [23, 56, 57]. The open-label ASCEND-1 trial showed that ceritinib benefits this population, with an ORR of 56%, median duration of response (DoR) of 8.3 months, and median PFS of 6.9 months [58]. Alectinib was tested in two phase II studies in crizotinib-resistant patients with measurable *ALK*-positive NSCLC [59, 60]. The NP28761 trial of 69 evaluable patients treated with alectinib showed an ORR of 48%, an estimated median PFS of 8.1 months, and a DoR of 13.5 months [60]. The NP28673 trial of 122 patients demonstrated similar efficacy of alectinib, with an ORR of 50% and a median PFS of 8.9 months [59]. Brigatinib was approved based on the ALTA trial, a global, phase II registration study of patients with *ALK*-positive NSCLC who were previously treated with crizotinib [57]. Patients who received brigatinib (180 mg once a day with 7-day, 90 mg lead-in) had a median PFS of 12.9 months [61]. Lorlatinib was recently granted FDA approval for patients previously treated with at least one ALK TKI, based on results from a global, multicohort phase II study [62, 63]. In 215 patients who were *ALK*-positive and who had received at least one previous ALK TKI, the ORR was 48% and the intracranial response rate in 89 patients with CNS lesions at baseline was 60% [63]. These targeted therapies are currently being evaluated in phase III clinical trials for use in the first- second-, and third-line settings (Table 4). In addition to these TKIs, other agents are in development. The National Clinical Trials Network ALK Master Protocol aims to tailor treatment based on the molecular mechanism of resistance. This basket trial will be opening soon.

Therapy with lorlatinib in *ROS1*-rearranged NSCLC is being assessed [64]. Emerging evidence suggests that cabozantinib is effective in patients with *ROS1*-positive NSCLC that has become resistant to crizotinib or ceritinib.

Nonsquamous Histology: Second-Line ICBs

With pembrolizumab moving to the first-line treatment setting, the role of ICBs in the second line has diminished; however, many important questions need to be addressed regarding the optimal placement of an ICB in the treatment life of a patient. Nivolumab is indicated for second-line use, regardless of PD-L1 status [10, 65, 66]. Nivolumab was tested against docetaxel in CheckMate-057, a phase III study that showed that nivolumab improved OS compared with docetaxel in patients with nonsquamous NSCLC (12.2 vs. 9.4 months). Although all patients derived clinical benefit from nivolumab, when data were stratified by PD-L1 expression, the magnitude of clinical benefit increased with increasing PD-L1 expression [65]. A PD-L1 complementary diagnostic biomarker test to measure PD-L1 expression is not required for prescribing nivolumab in patients with

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Table 3. Ongoing or planned phase III clinical trials of immune checkpoint blockers in metastatic NSCLC

NCT no. (trial acronym)	Agents	Line	Proposed *n*	Study design	Planned study completion date
Atezolizumab					
NCT02813785 (IMpower210)	Atezolizumab vs. docetaxel	2	563	Randomized, open-label in patients after failure with pCX; OS is primary objective	May 2019
Avelumab					
NCT02395172 (JAVELIN Lung 200)	Avelumab vs. docetaxel	2	792	Randomized, open-label in patients after failure with pCX; OS is primary objective	January 2023
NCT02576574 (JAVELIN Lung 100)	Avelumab vs. platinum doublet	1	1,095	Randomized, open-label; PFS and OS are primary objectives	April 2024
Nivolumab					
NCT02066636 (CheckMate 153)	Nivolumab	2	1,380	Randomized, open-label, phase IIIb/IV safety trial in patients who have progressed during or after ≥1 systemic regimen	January 2022
NCT02613507 (CheckMate 078)	Nivolumab vs. docetaxel	2	500	Randomized, open-label in patients after failure with pCX; OS is primary objective	January 2020
NCT02713867 (CheckMate 384)	Nivolumab	2+	620	Dose optimization study; PFS at 6 months is primary objective	June 2022
Pembrolizumab					
NCT02578680 (KEYNOTE-189)	pCX + pemetrexed ± pembrolizumab	1	570	Randomized, open-label in patients with nonsquamous disease	April 2019
Durvalumab					
NCT02453282 (MYSTIC)	Durvalumab ± tremelimumab vs. SoC pCX	1	1,118	Randomized, open-label in patients with no *ALK*- or *EGFR*-activating mutations; PFS is primary objective	December 2019
NCT02542293 (NEPTUNE)	Durvalumab + tremelimumab vs. SoC pCX	1	960	Randomized, open-label in patients with no *ALK*- or *EGFR*-activating mutations; OS is primary objective	March 2019
NCT02352948 (ARCTIC)	Durvalumab ± tremelimumab vs. SoC	3+	597	Randomized, open-label in patients with PD-L1-positive tumors; OS is primary objective	December 2018

Abbreviations: *ALK*, anaplastic lymphoma kinase gene; *EGFR*, epidermal growth factor receptor; NCT, National Clinical Trial; NSCLC, non-small cell lung cancer; OS, overall survival; pCX, platinum-based chemotherapy; PD-1, programmed cell death-1 receptor; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; SoC, standard of care.

nonsquamous NSCLC; however, the results of the complementary PD-L1 test may aid clinicians in deciding if nivolumab is appropriate for patients [7].

Pembrolizumab is FDA approved in the second-line setting for patients with metastatic, nonsquamous NSCLC and PD-L1 expression (TPS ≥1%) as determined by an FDA-approved, companion diagnostic test, with disease progression on or after platinum-containing chemotherapy, based on the phase II/III trial, KEYNOTE-010 [67]. In this trial, in which 70% of patients had nonsquamous histology, pembrolizumab (2 mg/kg group) significantly improved OS over docetaxel (10.4 vs. 8.5 months; p = .0008) [67]. The presence of microsatellite instability-high (MSI) tumors in NSCLC is rare and is not as routinely tested for as *EGFR*, *ALK*, *ROS*, *BRAF*, or *PD-L1* alterations; however, when the patient obtains full molecular profiling and the results show presence of MSI, then pembrolizumab is indicated and is the correct choice of therapy.

The anti-PD-L1 antibody atezolizumab has gained FDA approval for second-line use, regardless of PD-L1 status, based on the phase III OAK and phase II POPLAR trials [68, 69]. Among the 74% of patients with nonsquamous NSCLC, atezolizumab treatment (n = 313) was associated with longer median OS (15.6 months; 95% CI, 13.3–17.6) versus docetaxel-treated patients (n = 315; 11.2 months; 95% CI, 9.3–12.6); the OS benefit associated with atezolizumab was statistically significant (HR, 0.73; 95% CI, 0.60–0.89; p = .0015) [69, 70]. Among

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Table 4. Ongoing or planned phase III clinical trials of targeted therapy in locally advanced or metastatic NSCLC

NCT no. (trial acronym)	Agents	Line	Proposed *n*	Study design	Planned completion date
EGFR mutation					
NCT02474355 (ASTRIS)	Osimertinib	2	3,515	Real-world setting, interventional, in patients with *EGFR* T790M+ disease, OS is primary objective	April 2019
ALK rearrangement					
NCT02737501 (ALTA-1L)	Brigatinib vs. crizotinib	1	270	Randomized, double-blinded in patients with *ALK* mutations; PFS is primary objective	April 2021
NCT03596866	Brigatinib vs. alectinib	2	246	Randomized, open-label in patients with *ALK* mutations; PFS is primary objective	September 2023
NCT03052608	Lorlatinib vs. crizotinib	1	280	Randomized, open-label in patients with *ALK* mutations; PFS is primary objective	February 2023
NCT02838420	Alectinib vs. crizotinib	1	187	Randomized, open-label in Asian patients with *ALK* mutations; PFS is primary objective	December 2019
NCT02767804	Ensartinib vs. crizotinib	1	402	Randomized, open-label in patients with *ALK* mutations; PFS is primary objective	April 2020

Abbreviations: *ALK*, anaplastic lymphoma kinase gene; *EGFR*, epidermal growth factor receptor; NCT, National Clinical Trial; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

patients with the highest PD-L1 expression (PD-L1 expression on ≥50% tumor cells or ≥10% immune cells), OS was 59% greater in patients treated with atezolizumab versus docetaxel ($p < .0001$). Even in patients with no PD-L1 expression, atezolizumab provided a significant 25% improvement in OS versus docetaxel ($p = .0215$) [69]. Therefore, atezolizumab is approved regardless of PD-L1 expression levels, although a complementary PD-L1 test may provide useful information to guide treatment decisions [7, 11].

Nonsquamous Histology: Chemotherapy Second-Line Therapy

For patients who have received the pembrolizumab-carboplatin-pemetrexed combination in the first line, several options are recommended for second-line therapy, including docetaxel with or without the anti-VEGF antibody ramucirumab [7].

Nonsquamous Histology: Chemotherapy Third-Line Therapy

There is no standard therapy beyond second line, but single-agent chemotherapy is a reasonable approach.

SCC: First-Line Targeted Therapy and ICBs

Squamous histology requires different considerations for therapy selection. NCCN Guidelines recommend that molecular testing can be considered, including for *EGFR* and *ALK* genetic alterations, in patients with SCC if (a) the patient has never smoked, (b) small biopsy samples were used to assess histology, or (c) mixed histology was reported [7, 71]. *ROS1* and *BRAF* testing can also be considered. Molecular profiling can also be employed at the discretion of the treating physician. If actionable driver mutations are identified, treatment with the corresponding targeted therapy is appropriate [7].

In patients with SCC who have high PD-L1 expression (≥50% TPS), pembrolizumab is recommended for first-line intervention based on the KEYNOTE-024 trial described previously [34]. For the squamous subgroup ($n = 56$), there was a clear benefit of pembrolizumab to the risk of disease progression or death (HR, 0.35; 95% CI, 0.17–0.71) [34]. Pembrolizumab in combination with chemotherapy (carboplatin with paclitaxel or nab-paclitaxel) increased the objective response rate compared with chemotherapy alone (58.4% vs. 35.0%; $p = .0004$) in a first interim analysis from KEYNOTE-407 [72]. The median OS and PFS were also significantly improved with pembrolizumab plus chemotherapy combination over chemotherapy alone (OS, 15.9 vs. 11.3 months; $p = .0008$. PFS, 6.4 vs. 4.8 months; $p < .0001$) [72]. Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel was recently granted FDA approval as first-line therapy in patients with metastatic squamous NSCLC, based on KEYNOTE-407 trial data. Recent primary analyses from IMpower131 showed significantly increased PFS with atezolizumab in combination with carboplatin plus nab-paclitaxel compared with carboplatin plus nab-paclitaxel alone (6.3 vs. 5.6 months; HR, 0.71; 95% CI, 0.60–0.85; $p = .0001$) [73]. The OS data are immature.

SCC: First-Line Chemotherapy

In the absence of a genetic driver mutation or expression of PD-L1, NCCN recommends several chemotherapy options, including cisplatin plus carboplatin plus gemcitabine, or a taxane for first-line intervention [7]. SWOG S0819 reconfirmed that paclitaxel plus carboplatin remains a treatment option for unselected patients [74]. In this trial, which evaluated paclitaxel plus carboplatin with or without cetuximab, there was no benefit to the addition of cetuximab regardless of histology. In patients with squamous histology, the median OS was 8.0 months. Gemcitabine plus cisplatin is also a popular regimen based on a subgroup analysis of a noninferiority trial in which first-line cisplatin plus gemcitabine was compared with cisplatin plus pemetrexed in patients with advanced NSCLC. For patients

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with SCC, the OS was significantly improved with cisplatin plus gemcitabine versus cisplatin plus pemetrexed (10.8 vs. 9.4 months; HR, 1.23; 95% CI, 1.00–1.51; p = .05) [43]. This trial led to the removal of treatment of patients with squamous histology from the pemetrexed label. Combination carboplatin plus nab-paclitaxel is a reasonable option for SCC, based on a phase III subset analysis of patients with SCC that demonstrated a significantly higher ORR of 41% (95% CI, 34.7–47.4) with carboplatin plus nab-paclitaxel versus carboplatin plus/solvent-based paclitaxel (ORR, 24%; 95% CI, 18.8–30.1) [75]. Both continuation maintenance with gemcitabine and switch maintenance with docetaxel are category 2B recommendations in NCCN Guidelines for patients with SCC; both approaches have shown significant PFS benefits, although with no significant changes in OS [7].

Necitumumab plus cisplatin plus gemcitabine was removed from the NCCN Guidelines as a regimen for patients with metastatic SCC based on a lack of safety or efficacy benefit when compared with cisplatin plus gemcitabine and other available agents [7].

SCC: Second-Line ICBs

Nivolumab first received FDA approval for the second-line treatment of patients with squamous NSCLC, with no *EGFR* or *ALK* genomic tumor aberrations, based on CheckMate-017 [76]. Nivolumab significantly increased OS compared with docetaxel (9.2 vs. 6.0 months; p < .001) [76]. PD-L1 expression was neither prognostic nor predictive of efficacy in this patient population.

Pembrolizumab gained FDA approval for the second-line treatment of patients with metastatic NSCLC with squamous histology and PD-L1 expression (≥1% TPS), based on the phase II/III KEYNOTE-010 trial previously summarized [67]. In this trial, 21% of patients had squamous histology, and the improvement in OS associated with pembrolizumab was not statistically significant (HR, 0.74; 95% CI, 0.50–1.09), in part owing to the small population size involved.

Atezolizumab has FDA approval regardless of PD-L1 status based on the phase III OAK trial and the phase II POPLAR trial [11, 68, 69]. In the 26% of patients with squamous NSCLC in the OAK study, atezolizumab significantly increased OS versus docetaxel (8.9 months [95% CI, 7.4–12.8] vs. 7.7 months [95% CI, 6.3–8.9]; HR, 0.73 [95% CI, 0.54–0.98]; p = .0383) [69].

Given the positive data obtained when ICBs are combined with chemotherapy, second-line ICB usage will lessen.

Use of docetaxel plus or minus ramucirumab or afatinib should be entertained.

SCC: Second-Line Therapy in Patients Ineligible for Targeted Therapy or Immunotherapy

Afatinib has FDA approval for the treatment of patients with advanced squamous cell lung carcinoma whose disease progressed after treatment with platinum-based chemotherapy, based on LUX-Lung 8 trial results [77]. Docetaxel alone or in combination with ramucirumab is also an approved second-line option.

SCC: Third-Line Therapy

Therapeutic interventions following progression on a second-line treatment are at the discretion of the patient and doctor.

Diagnostic Testing

A biomarker test may help to identify patients who would benefit most from targeted therapy, ICBs, or a combination of therapies. Diagnostic tests require sufficient tissue and appropriate timing [78]. As the number of tailored therapies increases, there will be an increased need for testing algorithms that ensure all necessary molecular tests have been performed.

Molecular Testing

The joint recommendation issued by the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology strongly recommends molecular testing for *EGFR* and *ALK* in patients with advanced lung adenocarcinoma at initial diagnosis and at progression in those with lower-stage disease. Additionally, it is strongly recommended that physicians employ *EGFR* and *ALK* testing for tumors with histologies other than adenocarcinoma, if there are clinical features that suggest a higher probability of detecting an oncogenic driver [79]. The updated guidelines emphasize the importance of testing not only for *EGFR* and *ALK* but also for *ROS1*, *BRAF*, and other driver mutations [79]. NCCN Guidelines also strongly endorse broad molecular profiling [7]. Movement away from single testing to multiplex testing is encouraged to gain a comprehensive biological analysis of a patient's tumor.

Circulating Tumor Testing

Although tumor biopsy is considered the gold standard for molecular analysis, "liquid" biopsies obtained from peripheral blood or urine present an opportunity for a less invasive method to be used [80]. There are a number of clinically validated methods available for circulating tumor (ctDNA) testing [80, 81]. Although ctDNA testing has great promise, it does have limitations. The amount of ctDNA a tumor sheds is variable and can affect assay sensitivity [82]. The sensitivities of liquid-based assays are typically lower than those of tissue-based tests, and therefore there is a possibility of false negatives [83]. For example, a negative plasma test result for *EGFR* T790M warrants a rebiopsy to avoid missing an important actionable mutation [7, 83].

PD-L1 Testing

It is recommended that patients with metastatic NSCLC be tested for PD-L1 expression before first-line treatment [7]. The Dako PD-L1 IHC 22C3 pharmDX companion diagnostic for pembrolizumab is recommended for use in the first-line setting to identify patients with a TPS of ≥50% who are suitable for pembrolizumab monotherapy; however, institutions may use their own PD-L1 immunohistochemistry (IHC) testing platforms. The inherent variability in the use of different PD-L1 IHC testing platforms has been recognized by both industry and academia and has brought about the Blueprint PD-L1 IHC Assay Comparison Project that evaluated these tests for clinical comparability [84]. This study found that the assays cannot be considered to be interchangeable for the determination of PD-L1 status [84]. Of the four assays tested, all but the Ventana SP142 assay had comparable tumor cell staining, and immune cell staining was more variable than tumor cell staining [84]. PD-L1 testing is an imperfect biomarker because of its dynamic expression, which

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may be influenced by a variety of factors; thus, there is an ongoing and intensive search for other predictive biomarkers, such as TMB.

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Conclusion

Both targeted therapies and ICB agents have an important role in the treatment of NSCLC. In order to personalize therapy appropriately, careful molecular analysis of tumor samples is necessary to provide each patient with the best probability for prolonged survival. However, there is still much work to be done, and enrolling patients in clinical trials should be considered when making each treatment decision.

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